Franz Halberg's responses to questions posed for Life Sciences Publishing

by Ms. Reiko Ohsawa

Question 1:

WHAT BROUGHT BIOLOGICAL RHYTHMS SUCH AS THE CIRCADIAN TO THE ATTENTION OF PEOPLE IN BIOLOGY AND MEDICINE ? WAS THERE A SPECIFIC OCCASION ? PLEASE EXPLAIN THE REASON, REFERRING TO EPISODES AT THE START OF YOUR STUDY.

Answer:

Life or death. Circadian rhythms were brought to the attention of people in biology and medicine by the discovery of the hours of changing resistance and susceptibility. The stage of the body's rhythm at the time of exposure to a stimulus can account for the difference between convulsion or no convulsion, between a malignancy or no malignancy, even for the difference between life and death. For instance, when separate groups of inbred mice were injected at 4-hour intervals during several 24-hour cycles with the adrenocortical inhibitor, SU-4885, in the same dose, this drug killed at one circadian stage predictably, insofar as it did so reproducibly at the same circadian stage, practically all of the animals injected, whereas the same dose given to comparable animals at the opposite circadian stage (12 hours earlier or later) was survived without any ill effect.

Blood pressure increase or decrease from the same stimulus. The same circadian time dependence applies in humans to the response to the same kind of operation: it raises blood pressure in the morning but lowers it in the afternoon. Prof. Terukazu Kawasaki, Director of the Health Sciences Institute of Kyushu University in Fukuoka, Japan, demonstrated that the same amount of dietary salt per day affected blood pressure in a quite different way depending on how it was distributed among the three daily meals.

Chronobiology is not yet in the mainstream of health care, even if its research was supported by Prof. Teruo Omae, now at the National Center for Cardiovascular Diseases in Suita; by Prof. Takashi Yanaga of the Medical Institute of Bioregulation in Beppu; and by Prof. Takashi Sasaki of the Institute of Constitutional Medicine in Kumamoto. Dr. Yoshinori Koga of Kurume, Kyushu, and Dr. Yoichi Hata from Beppu were associated with our laboratory in Minnesota; along with others; they not only used automatic blood pressure monitoring early, but recognized the importance of rhythms. Chronobiology, not the in-itself insufficient automatic monitoring, is critical for health care. Before automatic monitors were available, many

Minnesotans and others around the world; Midori Matsuoka, a nurse in Kyushu; and Prof. Yoshihiko Chiba, of Yamaguchi University, and his wife Kazuko had demonstrated in Minnesota the spectrum of multifrequency rhythms, including circannual components in self-measurements using a conventional, manually operated sphygmomanometer. With automatic instrumentation, Prof. Kohji Tamura of Yamanashi Medical University, documented drug effects upon the circadian amplitude of blood pressure, that are important in the light of the high risk of catastrophic disease associated with an excessive circadian amplitude of blood pressure at all ages and irrespective of the 24-hour mean of blood pressure, as in the clinical entity of blood pressure overswinging or Circadian HyperAmplitudeTension, briefly CHAT.

We worked with Prof. Kawasaki, starting while he was a fellow at the U.S. National Institutes of Health (NIH) and thereafter in the major Kyushu-Minnesota study which represents the broadest and most extensive mapping of multifrequency endocrine and other rhythms thus far, involving over 50,000 radioimmunoassays, reported in over 50 publications with us. More than two dozen variables were mapped along the circadian, about-30-day (circatrigintan), about-yearly (circannual) and age scales, some of the major constituents of the chronome of a given variable. This Kyushu-Minnesota study, guided in Japan by Prof. Kawasaki, then in the department of Prof. Teruo Omae, served as the basis for the field of chronoepidemiology, later extended by contributions from Australia, Austria, Italy, Mexico, Spain, Sweden and the United Kingdom. This work revealed the importance of rhythms for early warnings of impending disease and that for certain purposes, such as cancer risk assessment, the circannual rhythm can be useful when the circadian is not directly informative (see answer to Question 2).

Question 2:

IN TERMS OF BIOLOGICAL CIRCADIAN RHYTHMS, ESPECIALLY IN HUMANS, WHAT IS THE COMMON UNDERSTANDING FROM THE RESULTS OF RECENT STUDIES?

Answer:

Chronomes include but are not restricted to circadians. Circadian rhythms are but one component of time structures, the chronomes of a variable (such as blood pressure), of a system (such as the cardiovascular system), of an organism, a habitat niche or of any other more restricted or broader system singled out for analysis: we must think of as many components as 1) the density, 2) the length of the data (series) and/or 3) the available prior reference values and other pertinent information permit, notably and often indispensably for interpreting the time-specified single measurement. Otherwise, apparently controversial results are likely to be misinterpreted: for instance, the same total dose per week of a Japanese drug, the immunomodulator lentinan, can enhance a cancer's growth or inhibit it, simply

as a function of the about- weekly as well as the about-daily timing of its administration.

Chronomes revolutionize our view of concern about circadian rhythms as they do in relation to jet lag or shift-work: the interval between consecutive shifts can play an unforeseen major role: twice-weekly, rather than weekly, schedule shifts in a laboratory animal were associated with a prolonged survival. A cardiologist, Yuzo Saito, his wife, and two sons, 6 months and 6 years of age, who came for a year to our laboratory from Yamanashi Medical College, showed with automatic monitoring that their circaseptan (about-weekly) rhythms of blood pressure and heart rate may not adjust for several weeks following a transmeridian flight to Minnesota. Those who decide shift-work schedules should be aware of this fact, which is pertinent to sleep disorders and seasonal affective disorders.

Family studies are invaluable, notably if they cover several generations. Dr. Yoshihiko Watanabe of the department formerly headed by Haruo Watanabe at Tokyo Women's Medical College has monitored his own blood pressure for over 8 years, and also the blood pressure of his grandmother, his wife (including her entire pregnancy, bracketed by a prior year and months thereafter), and his son. He gave a model for the rest of the world, having shown the changes with age in two of his cardiovascular chronomes longitudinally. In his son born at term, the about-weekly and half- weekly periodic components predominate over the circadian rhythm, exhibiting what we also find in some unicells, namely a sometimes larger amplitude of the about-weekly and/or about-half-weekly components as compared to that of the about-daily rhythm.

Circaseptans have been the subject of intensive study by Dr. Keiko Uezono at Kyushu University. As noted in the response to question 1, also at Kyushu University, Prof. Terukazu Kawasaki, had shown in the study started with Prof. Teruo Omae that the circannual amplitude of several hormones was a gauge of the risk of several civilization diseases. Circulating aldosterone was the major interest of Profs. Omae and Kawasaki. On their insistence, which led to success, aldosterone determinations were included in the originally only U.S.-financed cancer study. The success was the finding that the circannual amplitude of aldosterone correlated negatively with cardiovascular disease risk; the circannual amplitude of prolactin correlated negatively with breast cancer risk; and the circannual amplitude of TSH correlated positively with breast cancer risk. Correlations of the circannual amplitude of prolactin and TSH were later found in another study in association also with prostate cancer. The Kyushu-Minnesota study opened the door toward prevention.

These examples illustrate that our make-up in time as a whole (our chronomes) are the blueprint of health and the complement to the genome. Many hundreds of millions of dollars are being spent on the genome with the hope of introducing gene therapy for various diseases. For this to be optimal and in some cases even to be considered, as in seeking the genetics of CHAT (see above), a linear biochemistry

has to be replaced by a chronobiochemistry. The mapping of multifrequency rhythms and of other components of the chronome are the keys to maintaining good health and to recognize an elevation of the risk of disease in health so that preventive measures are instituted whenever warranted (that is whenever early warning signs are identified by means of early chronome (e.g., rhythm or trend or chaos) alterations before the onset of actual disease.

Question 3:

WHAT MECHANISM OF BIOLOGICAL RHYTHMS COORDINATES CIRCADIAN RHYTHM SEEN IN VARIOUS FACTORS OF THE CIRCULATORY SYSTEM SUCH AS BLOOD PRESSURE AND HEART RATE? WHAT IS THE SIGNIFICANCE OF CIRCADIAN RHYTHMS TO SUCH FACTORS OF THE CIRCULATORY SYSTEM?

Answer:

The mechanisms of chronomes in biology and in the circulation in particular (which include trends and chaos with rhythms) are feedsidewards rather than feedbacks. Feedsidewards are interactions among 3 or more entities at the cellular, organ-system and/or organismic levels and/or interactions among these levels; they lead to predictable sequences of stimulation, no-effect and inhibition by one periodic entity such as the pineal upon the interaction of two others, such as the pituitary and the adrenal. Cinematography at the cellular level reveals that even a single myocardial cell taken into culture exhibits a chronome: the beating in vitro shows not only a circadian rhythm, but also rhythms with frequencies higher and lower than circadian, all in the absence of any motor activity of the entire organism, the factor believed to be the major "mechanism" of circadian rhythms. At the organism level, the actual mechanisms of rhythms in systolic, mean arterial and diastolic blood pressure and heart rate are at least in part different. The systolic blood pressure can show a different circadian period than motor activity in a boy studied around the clock for a month. Systolic blood pressure, not heart rate, increases each day around mid-sleep (before awakening).

My early work pointed to the adrenal cortex as a major mechanism responsible for the circadian rhythm in blood eosinophils, and thus in hormones depressing that count, such as adrenal corticosteroids, while the circadian rhythm in serum iron persisted after removal of both adrenals in the very patients whose eosinophil rhythm could not be detected. By 1959, by stepwise ablations, we also found that the brain played a major role. Prof. Terukazu Kawasaki has documented the circadian rhythm in plasma renin activity (and in many other hormones) under controlled conditions; it will be important to look at human renin as a chronome since, in the rat, renin production in vitro undergoes a circannual rhythm, with a change of about 60% above and 60% below the mean (a 120% change around the mean equated to 100%).

Remove-replace approaches are helpful. The circadian rhythm in heart rate in one study (but not in another and not that in blood pressure) persists after a histologically validated bilateral suprachiasmatic nuclear (SCN) lesion. The circadian rhythms in water-drinking, in motor activity and in cardiac arrhythmias also have not been detected in rodents with histologically validated SCN lesions. Persisting after SCN ablation are rhythms in core temperature, DNA formation and mitosis throughout the digestive tract. The adrenal cortex and the SCN account for some, but not all circadian rhythms.

A task ahead for researchers of the circulatory system is to use the chronomes to better define people, described by us with Dr. Kawasaki and Dr. Frederic C. Bartter (of Bartter syndrome fame), who respond to a load of dietary sodium with a decrease, others who respond with an increase, and still others with no statistically significant change in blood pressure. After accounting for regression to the mean [TRANSLATOR: THIS IS A STATISTICAL TERM THAT CANNOT BE TRANSLATED LITERALLY], one can look at the dynamic endocrine rhythm characteristics in these three groups, along with studies of underlying metabolic chronomes. This important task is one of the many opportunities where the mapping of genomes and chronomes is complementary. A beginning has been made by the studies on Dahl rats, also affected differently by sodium intake, conducted by Dr. Keiko Uezono of Kyushu University (with whom we cooperated in over 40 publications). Another important direction are the studies of Prof. Kawasaki in Japan and Nepal that await extension to chronomes, whereby they could prove to be of key importance. Combining the study of the genetics with the chronobiology of vascular disorders may clarify, among others, the adjective "essential" used to describe the condition of idiopathic hypertension.

Question 4:

HOW DO CIRCADIAN AND OTHER RHYTHMS IN THE CIRCULATORY SYSTEM INFLUENCE HYPERTENSION, ARRHYTHMIA, MYOCARDIAL ISCHEMIA, CEREBRAL INFARCTION, ETC? WHAT IS THE SIGNIFICANCE OF THESE RHYTHMS? Answer:

Different adverse vascular outcomes -- various kinds of stroke or arrhythmias -- have different times of highest susceptibility pointing to different, thus testable mechanisms. A case in point is an overswinging or CHAT, which is associated with a 720% increase in the risk of ischemic stroke in data of Associate Prof. Kuniaki Otsuka of the Tokyo Women's Medical College, Daini Hospital. Is this an overcompensatory mechanism by a circulatory system that cannot fully meet demands? In the stroke-prone rat of the late Prof. Kozo Okamoto a large circadian amplitude of the blood pressure precedes the elevation of the 24-hour mean of blood pressure. This applies to humans, as shown by Dr. Yuji Kumagai of Kitasato University East Hospital (Kanagawa, Japan); he formed three groups according to their left ventricular mass index, obtained by echocardiography; the circadian amplitude was elevated in the middle group, while the MESOR in this group was

acceptable. This finding is in keeping with the observation that CHAT is most frequent in patients whose MESOR is around 130-140 mm Hg. CHAT is found more often prior to the occurrence of (than during) overt MESOR-hypertension.

Patients with too large a pulse pressure (indicating perhaps a failing compliance), or with a reduced heart rate variability are also at an increased risk for vascular complications. Magnetic disturbances can reduce heart rate variability and may be one mechanism through which an increased risk of myocardial infarction may come about. Preventive measures are warranted, with the chronome maps of Dr. Kawasaki and Dr. Uezono's disease risk gauges in mind.

Question 5:

WHAT CHRONOCARDIOTHERAPEUTIC SUBJECT(S) DO YOU THINK SHOULD BE DEVELOPED IN THE FUTURE? WHAT DO YOU EXPECT OF JAPANESE RESEARCHERS?

Answer:

Telemetered beat-to-beat monitoring of blood pressure and heart rate is feasible in the experimental laboratory. It has also been carried out in ambulatory humans for over a year. Until miniaturized, truly unobtrusive devices for continuous longitudinal monitoring are more generally available for humans, several lines of investigation may be very meaningful. First is focus on CHAT, the excessive circadian amplitude of blood pressure associated with a very large increase in the risk of ischemic stroke and nephropathy. This condition can affect MESOR-normotensive individuals. For them, non-pharmacologic means such as chronobiologically timed autogenic training may be a first treatment. Dr. Takenori Kikuchi at Daini Hospital in Tokyo has made a start without timing, but using a control chart for assessing results.

Control charts could be handled by the individual patient who measures as rarely as three times a day. Education will be critical for the population in general and for those with blood pressure disorders in particular, to realize that catastrophic disease can be prevented by the early institution of preventive measures prompted by home measurements that are not carried out at times of convenience, but rather at times of pertinence for the given patient, and that are checked readily by programs implemented on personal computers at home. These can also indicate when a central computer and, if need be, the chronobiologically trained nurse, the chronutrix, or physician may be consulted. Dr. Kawasaki in cooperation with a motivated chronutrix, Midori Matsuoka, has set an example in this context.

Chronotherapy aims at peak action at the "right" stage of the circadian and other cycles and must not be replaced by "24-hour coverage". One of the most important lessons for the public, the physician and the drug industry is the large difference

that may exist between the chronopharmacokinetics and the more critical chronopharmacodynamics of a drug. But chronobiology is a lot more than interventions timed for a better treatment of overt diseases: It enables prevention.

Question 6:

PLEASE DESCRIBE THE CONCEPTION OF "CHRONOME", THE CONCEPT YOU BROUGHT FORWARD. WHAT KIND OF HOPE DO YOU HAVE FOR THIS TERM?

Answer:

Three entities have been identified to constitute a broad time structure (the chronome): multifrequency rhythms, trends (as a function of age and also as a function of disease risk or response to treatment), and the as-yet unresolved variation (noise). The latter includes some measures of fractal scaling such as the correlation dimension of deterministic chaos, shown to exhibit circadian rhythms and also to exhibit trends as a function of both disease and age so that the three entities of the chronome all interact. Focus should be directed at the chronome as a whole.

When I coined the term "circadian", I did not know that the relative importance of the about-weekly or half-weekly component vs. the circadian component varies as a function of age, and also as a function of the development of hypertension. Focus on more than one component, upon the chronome (see answer to question 2), refines our tools to spot early rhythm alteration and to institute preventive measures even earlier, at a time when health can be maintained, rather than having to cure the fact of disease. Either with longitudinal self-measurement or with more sophisticated miniaturized instrumentation yet to be developed, to be used on a broad scale, the concept of recycling -- of analyzing more and more chronome components as the data accumulate -- should be followed-up, so that a continuous history from the physiologic monitoring can complement the continuous physical self-examination.

The pacemaker-cardioverter-defibrillator, like the pacemaker, focuses upon the sick. There are also automatic drug administration devices. Now the loop will have to be closed to act preventively with implanted sensor prototypes functioning for over a year in ambulatory humans, as yet only as diagnostic tools. In the interim, instrumentation systems are necessary to act preventively, starting at birth. This is the task of Dr. Germaine Cornelissen's chronome initiative, with devices in the home.

Japan was first in a large international study focusing on the risks of different conditions under the leadership of Prof. Teruo Omae and Prof. Terukazu Kawasaki, now joined by Associate Professor Keiko Uezono, the Japanese holder of the International Chronobiologia Award. Japanese industry has made it possible worldwide to gather chronobiologic evidence, under the leadership of Masayuki

Shinoda, President, and Yuji Kawabata of Colin Electronics in Komaki, near Nagoya. My advice to Japanese researchers is to realize that four and a half decades of work on the chronome are available in our Minnesota laboratory, as unique reference standards and with a number of computer methods that allow the "recycling" of continuously monitored data covering years; these procedures provide warnings of disease risk elevation with a very great lead, sometimes at birth. We discovered that the circadian amplitude of neonatal blood pressure is already enlarged following the exposure to betamimetic drugs in the womb. This effect is not transient, but is demonstrable as an enlarged circadian amplitude and also as an enlarged left ventricular mass index in the adolescent.

Education in chronobiology should become worldwide a feature of health literacy that can prevent much catastrophic disease with "smart" devices that not only make the failing heart go again, but that help us prevent it from failing. Several international resolutions have advocated that the current recommendation by the World Health Organization for a subject to return only in two years if single measures are below 130/85 mm Hg systolic/diastolic is outdated.

In the Annals of the New York Academy of Science, Dr Germaine Cornelissen of the University of Minnesota (with whom we formulated the chronome concept and who during the past 20 years cooperated with Japanese investigators in designs and analyses) has impeached current practices relying on casual measurements. She offers recommendations, accepted at a consensus meeting of the International Society for Research on Civilization Diseases and the Environment which led to the resolution of monitoring for 7 days as a start to screen the blood pressure and heart rate status of individuals. When a disorder is found, the gold standard is lifetime monitoring as long as there is only a palliative treatment.

Today, we monitor parking ramps and supermarkets. Let us get the instrumentation, invasive and non-invasive, to monitor ourselves cost-effectively with strategic sampling, starting at birth. Dr. Cornelissen's chronome initiative deserves a place comparable to the genome project. It could be the most ambitious and the most important Japanese hankaigi for the prevention of catastrophic diseases.

Dr. Kawasaki has proved that over 50,000 endocrine and other assays can be completed with no single shipment lost. He is not only a rigorous physician-scientist-investigator but also capable of administering a complex international study. The next step is to test with long-term outcomes the merits of non-pharmacologic and pharmacologic interventions designed to correct deviations in the whole chronome in chronobiologic trials, with stroke prevention in the case of an excessive circadian blood pressure amplitude (CHAT or overswinging) as the first step.

In the USA, the cost of stroke is estimated to be $30 billion/year, not to mention the suffering after a massive stroke. It is costly and devastating in Japan as well. A

hankaigi to prevent catastrophic diseases such as stroke by focus on chronome alteration could bring chronobiology into the main stream of medicine.

Question 7:

IS THERE ANY INTERNATIONAL MOVEMENT FOR THE DISCUSSION AND PREPARATION OF GUIDELINES OR STANDARDS FOR THE DIAGNOSIS AND TREATMENT OF BLOOD PRESSURE DISORDERS BASED ON AMBULATORY MONITORING?

Answer:

This question can be answered in the affirmative for a chronobiologic approach based on data which we received from around the world, including some from a hankaigi in Japan under the direction of Prof. Terukazu Kawasaki. An extension of these data is very important to construct reference values in health for the interpretation of single values that are specified not only in terms of the circadian scale but also of other rhythm scales such as the week and the year. Such studies are also important to derive reference values (chronodesms) for circadian (and other) rhythm characteristics. Detailed guidelines are available with proper references under the heading "Toward a chronobiologic blood pressure screening clinic" on pp. 33-44 of Otsuka K., Cornelissen G., Halberg F. (eds.). Chronocardiology and Chronomedicine: Humans in Time and Cosmos (Life Science Publishing, Tokyo, 1993, 147 pp.).

Circadian chronodesms from womb to tomb are being mapped for Japanese and Caucasians as part of an international womb-to-tomb chronome initiative. The minimal fully automatic or manually activated measurement series should cover 7 days, with a sampling rate of at least one measurement every 3 hours in the case of manual measurements, and preferably of at least 2-4 measurements per hour in the case of automatic monitoring. Some reference values are already available in different age groups and will need to be refined to focus on individuals at low vascular disease risk with an assessment of long-term outcomes.

One of the biggest problems lies not so much in the derivation of such reference values (which can be well approximated with relatively few data series for a given population), but rather in their dissemination and their endorsement by established institutions such as the World Health Organization. This is where Dr. Teruo Omae, as Japan's representative, could play a central role.